Dialysis Therapy in the United States: A Historical Perspective

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There can be no better testament to the sorry state of the quality of hemodialysis in the United States than a brief health note that appeared at the top of page 13 of the September 13, 1998, issue of *Parade* magazine. This brief note of advice from Health Notes editor, Dr. Isadore Rosenfeld, appears in *Parade* under the title: "Dialysis: Not good for Longevity." The message to U.S. dialysis patients: Get a transplant as soon as possible because the longer you stay on dialysis, the greater your chances are of premature death. The same advice was given to patients in the late 1970s [1].

Think what that brief statement does for the morale of sick, underdialyzed, hypertensive hemodialysis patients across the United States who, because of a shortage of donated kidneys, cannot get off dialysis for many years. Moreover, kidney transplantation is not an ultimate solution for all patients; some patients are not accepted for transplant for various reasons, and some patients reject the kidney quickly [1]. All failures of other renal replacement therapies (transplantation, peritoneal dialysis) end up on hemodialysis.

In my view, the quality of hemodialysis care in the United States began to deteriorate when renal patients became eligible for Medicare coverage in 1972. The questions that I pose herein are twofold: What went wrong with the quality of hemodialysis in the United States, and can that quality be improved?

There are two basic ways that hemodialysis affects the health and longevity of the patient with end-stage renal disease. The first is by the removal of uremic toxins; the second is by using that powerful tool, ultrafiltration, to normalize blood pressure (BP).

The history of toxin removal

During the 1960s and early 1970s, prescribing the correct dose of dialysis was pure guesswork. Criteria for adequate dialysis were based on clinical grounds: eradication of uremic manifestations and adequate rehabilitation [2,3]. Any uremic manifestation, including elevated blood pressure, was considered inadequate dialysis in the early 1970s [4]. The first objective measurement of the dose of dialysis was serial measurement of nerve conduction velocity, which would slowly return toward normal if the dose of dialysis was sufficient [5]. A combination of nerve conduction velocity above lower normal range, serum albumin above 3.0 g/dL, and hematocrit over 20% without blood transfusions correlated well with clinically adequate dialysis and was considered an objective index of dialysis adequacy [6]. In the 1970s, easier-to-use methods were devised to measure the dose of dialysis, including the dialysis index [7] and the Kt/V index [8]. In this presentation I will refer to another dose index, the urea reduction ratio (URR). The URR is the percent drop in blood urea nitrogen during a single dialysis session. Not surprisingly, tremendous technical advances in hemodialysis therapy have been made, particularly with the introduction in the late 1960s of the hollow fiber hemodialyzer design [9,10]. These advances have made it possible to deliver increasingly larger doses of dialysis. Yet in the 1990s most patients in the United States still are underdialyzed. How is this possible?

In the early 1980s a tendency to shorten dialysis time became prevalent in dialysis centers in the United States. This tendency stemmed from the interpretation of the results of a large-scale study in the early 1980s, the National Cooperative Dialysis Study [11]. In this study the correlation between outcome and longer treatment time showed a nonsignificant (p = 0.06) trend, but there was a close correlation between patient outcome and Kt/V. Although the hemodialysis community was advised to shorten dialysis time only with great caution [12], a reanalysis of the study results published two years later led to the conclusion that the appropriate total dose of dialysis, expressed as Kt/V, should be delivered to the patient and that there is no improvement of results with Kt/V above 0.9 – 1.0 [13]. Time of dialysis was not analyzed separately as a factor. Because V is essentially stable in a patient, the dose of dialysis depends on K and t. If so, it was widely accepted that dialysis time may be decreased with impunity provided that it is compensated with a proportional increase of dialyzer clearance. Since a shorter dialysis session is more efficient and more profitable, it has great appeal to dialysis centers in the United States. Add to that the appeal that the short dialysis session has to the misinformed U.S. dialysis patients and you have a very destructive combination. Dialysis patients demanded the shortest possible dialysis sessions, and dialysis centers were eager to follow patients' demands.

Fortunately for dialysis patients in Japan, reimbursement was based on the length of each dialysis. This seemingly simple difference accounts in part for the increased length of survival among Japanese dialysis patients [14], where the

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dialysis dose was both higher and delivered over a longer time. Lengthening the time that the prescribed dose of dialysis is delivered increases the removal of larger molecules and reduces the chance of a dose-lowering adverse episode.

This misuse of powerful hemodialysis technology as a device to shorten dialysis session times without increasing dialysis dose reached a maximum as reflected in patient survival in the United States in the 1980s when dialysis session times as short as 2 – 2.5 hours were tried. The adjusted U.S. annual mortality rate (the number of deaths per 1000 patient-years at risk) was 26.2 deaths, and the URR was 55% – 60% [14]. Beginning in 1990, some increase in session time accompanied by an increase in dialysis dose from a URR of 60% to 67% was associated with a fall in adjusted annual mortality rate from 26.2 to 22.9 by 1995 [15].

In a recent article, Owen *et al*. [16] present an elegant statistical analysis of the effect of dialysis dose on survival. In Table 4 their data demonstrate an inverse correlation between patient mortality and dialysis dose. The table has four lines of dosage which increases from less than 55% to more than 65% with an expected decrease in mortality from 21% to 17%.

My questions are these: Why are we reporting data on the relationship between degrees of severity of uremia and rate of mortality in the late 1990s when uremia easily is cured by an adequate dose of dialysis? Should we not be studying the effect of various dialysis dosage levels on the physical and mental health of dialysis patients? After all, rehabilitation, not survival, should be the goal of a treatment program fully funded by Medicare.

Contrast the above dialysis dosage levels with the average URR of 78% in 772 patients studied over the past 30 years in the dialysis unit in Tassin, France. An expected consequence of this higher dose of dialysis is that uremic malnutrition is eliminated in patients on long-term dialysis in Tassin. The average increase in dry weight among a group of 61 patients studied recently is 1.9 kg at one year and 3.8 kg at two years [17].

Using urea as a marker upon which to base dialysis dose is misleading. Although Charra *et al*. [18] provide a high dose of dialysis as expressed by Kt/V, they found that urea Kt/V per session was not a significant predictor of survival, whereas the dialysis index [7], which reflects both small and middle molecule removal, did correlate with survival. This finding comes as no surprise, since urea is not a uremic toxin. The importance of longer dialysis time for decreasing morbidity and mortality was again recently confirmed by the Japanese experience [19], showing that increasing time by a factor of 1.5 leads to a fourfold decrease in mortality. Moreover, this study also found that the survival plateau was not achieved at 5 hours of dialysis.

High morbidity and mortality reported in the early 1990s in U.S. dialysis patients prompted provocative editorials by Nosé warning the Japanese not to emulate short dialysis as practiced in the United States [20,21]. Locatelli and Manzoni [14], looking at the data of the Lombardy Registry of Dialysis and Transplantation, noted a trend to shorten dialysis time in recent years. They considered it a dangerous trend and implored nephrologists to avoid mistakes experienced in the United States. The title of the paper alludes to the statement by Hegel in his introduction to *Philosophy and History* (1832): "What history teaches is this: that people have never learned anything from history or acted on principles deduced from it."

The history of BP control

Table I shows the survival history of all patients who started on dialysis at the University of Washington prior to 1968. What these patients had in common was that they all became or remained normotensive after starting dialysis therapy.

From the outset, our therapeutic philosophy included trying to control hypertension simply because it made good therapeutic sense. Perhaps this posture was in part derived from an experience with our very first patient, Mr. Clyde Shields, who developed malignant hypertension 3 months after starting dialysis therapy. Because we had nothing else to offer, we chose to try to save his life by using aggressive ultrafiltration to control his hypertension, which we succeeded in doing in about 2 months. Although he remained normotensive for the next 11 years, he died of a massive myocardial infarction while on dialysis in his home in 1971. At autopsy he had severe atherosclerosis, something that we did not pay enough attention to at the time. Indeed, it was not until later that it became clear that accelerated atherosclerosis was a major threat to prolonged survival of patients on dialysis therapy [22,23].

In the 1960s and 1970s many groups resorted to bilateral nephrectomy to control hypertension [24,25]. A particularly high proportion of patients with hypertension not responding to "volume control" and requiring bilateral nephrectomy were reported by authors using infrequent dialysis (8 hours twice weekly on coil dialyzers or once weekly peritoneal dialysis) [26]. The authors using long and frequent dialysis (3 times weekly) reported that hypertension could be much more easily controlled without resorting to nephrectomy [27,28]. In the mid-1970s, Twardowski reported that blood pressure could be controlled in all 14 studied patients without use of blood pressure medications by utilizing appropriate length and duration of dialysis (3 times weekly, 8 – 9 hours, and 4 times weekly, 6 – 7 hours, on coil dialyzers) [29].

In the meantime, during the 1980s attention shifted to the equally important question of determining the correct dose of dialysis. The importance of blood pressure control was all but forgotten and has remained in the background until the present day [30]. The one major exception was Guy Laurent's dialysis unit in Tassin, France.

The Tassin experience with BP control

Beginning with their first publication in 1983 [31], the Tassin dialysis program gradually evolved into the gold standard for long survival and low morbidity, especially from hypertension-

TABLE I Survival of all early University of Washington dialysis patients[a]

	Died
C.S.	11 years. 1960–72. Hemodialysis only. Died of myocardial infarction.
H.G.	27 years. 1960–1987. Transplant in 1968. Died accidental death.
R.H.	14 years. 1960–1974. Dialysis only. Massive uremic neuropathy at the outset from which he eventually died.
J.A.	36 years. 1961–1996 Dialysis only. Died of complications of chronic renal failure.
	Surviving
R.E.	Dialysis started 1963. Cadaveric transplant in 1987.
P.L.	Dialysis started 1967. Cadaveric transplant in 1991. Back on hemodialysis since 1997.
N.S.	Dialysis started 1968. Two cadaveric transplants, two successful pregnancies. Currently on continuous ambulatory peritoneal dialysis.

[a] The reason that we treated so few patients was due to the fact that after 1962, all new patients were accepted for treatment at the Seattle Artificial Kidney Center.

induced atherosclerotic complications among patients on hemodialysis [32,33]. Using their drug-free dry weight method of BP control [34,35], more than 90% of 772 patients studied over the past 30 years remained normotensive [33]. Other investigators have successfully employed the drug-free dry weight method of BP control to normalize BP in the dialysis patient [36]. Yet this proven method of normalizing BP in the dialysis patient continues to be ignored, especially in the United States, where the atherosclerotic complications of hypertension now are reaching epidemic proportions because hypertension is so poorly controlled [15,37,38].

In response to this crisis, a National Kidney Foundation task force published an extensive review of this subject together with therapeutic recommendations and suggestions of areas for future clinical investigation [39]. Unfortunately, contrary to my recommendations, this report failed to discuss and acknowledge that the Tassin drug-free dry weight method of BP control is the only method that has proven successful in dialysis patients. Furthermore, while recommending several areas for future clinical investigation, the task force failed to specifically recommend that a U.S. clinical study be funded to investigate further the drug-free dry weight method of BP control in the dialysis patient. Whether or not this study is done, hypertension will remain uncontrolled among dialysis patients in the United States until the drug-free dry weight is adopted. Antihypertensive medications have proven to be totally ineffective as a means of treating hypertension in dialysis patients [40].

Comment

Until the U.S. dialysis community accepts provision of the largest practical weekly dose of dialysis and the absolute control of hypertension as its two most important therapeutic goals, it will not be reasonable to ask Dr. Rosenfeld to change his advice to dialysis patients.

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